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ARMY ENVIRONMENTAL HYGIENE AGENCY ABERDEEN PROVING GR--ETC F/6 6/20
TOPICAL HAZARD EVALUATION PROGRAM OF CANDIDATE INSECT REPELLENT--ETC(U)
APR 80 A W SINGER

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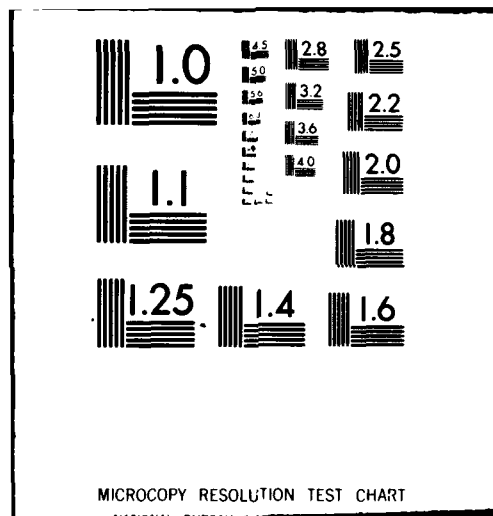
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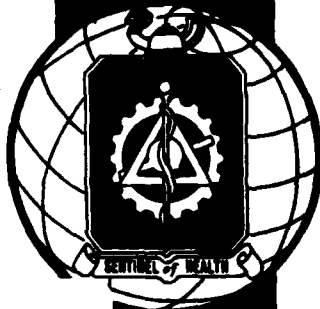
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UNITED STATES ARMY
ENVIRONMENTAL HYGIENE
AGENCY

ABERDEEN PROVING GROUND, MD 21010

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6 TOPICAL HAZARD EVALUATION PROGRAM OF CANDIDATE INSECT REPELLENTS
AI3-36325, 1-(CYCLOHEXYLCARBONYL)HEXAHYDRO-1H-AZEPINE,
AI3-36326, N,N-DIPROPYL-CYCLOHEXANECARBOXAMIDE,
AND AI3-36328, 1-((6-METHYL-3-CYCLOHEXEN-1-YL)CARBONYL)-PYRROLIDINE.
STUDY NOS. 75-51-0833-80, 75-51-0834-80, AND 75-51-0835-80
OCTOBER 1975 - APRIL 1980

9 Final rept. Oct 75 - Apr 80

10 Allan W. Singer

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) Preliminary hazard evaluations of the above candidate repellents were performed by means of laboratory animal studies using rats, rabbits, and guinea pigs. None of the compounds caused any phototoxic or skin sensitization reactions, nor were they acutely toxic by ingestion. AI3-36325 and AI3-36328 caused moderate corneal and conjunctival injuries, however, AI3-36326 and AI3-36328 caused mild skin irritation.		

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U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MARYLAND 21010

CPT Singer/lm/AUTOVON
584-3627

18 JUL 1980

HSE-LT/WP

SUBJECT: Topical Hazard Evaluation Program of Candidate Insect Repellents
AI3-36325, 1-(cyclohexylcarbonyl)hexahydro-1H-Azepine,
AI3-36326, N,N-dipropyl-cyclohexanecarboxamide, and
AI3-36328, 1-[(6-methyl-3-cyclohexen-1-yl)carbonyl]-Pyrrolidine,
Study Nos. 75-51-0833-80, 75-51-0834-80, 75-51-0835-80,
October 1975 - April 1980

Executive Secretary
Armed Forces Pest Management Board
Forest Glen Section, WRAMC
Washington, DC 20012

A summary of the pertinent findings and recommendations of the inclosed report follows:

Preliminary hazard evaluations of the above candidate repellents were performed by means of laboratory animal studies using rats, rabbits, and guinea pigs. None of the compounds caused any phototoxic or skin sensitization reactions, nor were they acutely toxic by ingestion. AI3-36325 and AI3-36328 caused moderate corneal and conjunctival injuries, however, AI3-36326 and AI3-36328 caused mild skin irritation. Due to the skin and corneal irritation, it was recommended that AI3-36325, AI3-36326, and AI3-36328 be handled with caution near the face and eyes.

FOR THE COMMANDER:

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DEPARTMENT OF THE ARMY
U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MARYLAND 21010

HSE-LT/MP

TOPICAL HAZARD EVALUATION PROGRAM OF CANDIDATE INSECT REPELLENTS
AI3-36325, 1-(CYCLOHEXYLCARBONYL)HEXAHYDRO-1H-AZEPINE,
AI3-36326, N,N-DIPROPYL-CYCLOHEXANECARBOXAMIDE,
AND AI3-36328, 1-[(6-METHYL-3-CYCLOHEXEN-1-YL)CARBONYL]-PYRROLIDINE,
STUDY NOS. 75-51-0833-80, 75-51-0834-80, AND 75-51-0835-80
OCTOBER 1975 - APRIL 1980

1. AUTHORITY.

a. Letter, US Department of Agriculture - Agricultural Research Service, Southern Region, Insects Affecting Man Research Laboratory, Gainesville, Florida, 31 October 1975.

b. Memorandum of Understanding between the US Army Environmental Hygiene Agency; the US Army Health Services Command, the Department of the Army Office of The Surgeon General, the Armed Forces Pest Control Board; and the US Department of Agriculture, Agricultural Research, Science and Education Administration, titled, Coordination of Biological and Toxicological Testing of Pesticides, effective 23 January 1979.

2. REFERENCE. Toxicology Division Procedural Guide, US Army Environmental Hygiene Agency (USAHA), 1972, revised 1976.

3. PURPOSE. The purpose of this program is to provide guidance for further entomological testing of the candidate insect repellents AI3-36325, AI3-36326, and AI3-36328.

4. SUMMARY OF FINDINGS. Hazard evaluations of the above candidate repellents were conducted by this Agency using New Zealand White rabbits for skin and eye studies, Hartley guinea pigs for a skin sensitization study, and Sprague-Dawley rats for determination of oral toxicity. A tabular presentation of animal toxicity data developed in this Agency follows:*†

* In conducting the studies described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," US Department of Health, Education and Welfare Publication No. (NIH) 74-23, revised 1978.

† The experiments reported herein were performed in animal facilities fully accredited by the American Association for the Accreditation of Laboratory Animal Care.

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TABLE. PRESENTATION OF DATA

Test	Results	Interpretation
<u>SKIN IRRITATION STUDIES</u>		
<u>Rabbits</u>		
Single 24-hour application to intact and abraded skin of New Zealand White rabbits.	Compound AI3-36325 did not cause any irritation of the intact skin or of the skin surrounding an abrasion.	USAEHA Category I (ref Appendix).
0.5 mL of each technical grade compound applied to each of six rabbits.	Compounds AI3-36326 and AI3-36328 caused mild irritation of intact and abraded skin.	USAEHA Category II (ref Appendix).
<u>EYE IRRITATION STUDIES</u>		
<u>Rabbits</u>		
Single 24-hour application of 0.1 mL of each technical grade compound to one eye of each of six New Zealand White rabbits.	Compound AI3-36326 caused mild irritation to corneal and conjunctival tissues.	USAEHA Category C (ref Appendix).
	Compounds AI3-36325 and AI3-36328 caused moderate irritation to the corneal and conjunctival in all rabbits.	USAEHA Category E (ref Appendix).
<u>APPROXIMATE LETHAL DOSE (ALD)</u>		
<u>Oral</u>		
Rats (male) - no diluent	ALD for AI3-36325: 1900 mg/kg.	None of the compounds present a lethal hazard from accidental ingestion.
	ALD for AI3-36326: >4300 mg/kg.	
	ALD for AI3-36328: >4300 mg/kg.	

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Test	Results	Interpretation
<u>PHOTOCHEMICAL SKIN IRRITATION STUDIES</u>		
<u>Rabbits</u>		
A single 0.05 mL application of a 25 percent (w/v) solution of each compound and a 10 percent (w/v) Oil of Bergamot solution (positive control) in 95 percent ethyl alcohol were applied to the intact skin of six rabbits. Five minutes after application, the rabbits were exposed to UV light (365 nm) for 30 minutes at a distance of 10-15 cm.	None of the 25 percent solutions in ethanol caused a photochemical irritation reaction under test conditions.	None of the compounds caused photochemical irritation reactions under test conditions and none are expected to cause photochemical irritation in humans.
	Both AI3-36325 and AI3-36326, however, caused a mild primary skin irritation to both the irradiated and nonirradiated skin as applied.	Ethanol solutions of AI3-36325 and AI3-36326 may cause primary irritation to human skin.
<u>Control</u>		
Following UV exposures of the rabbits, 0.05 mL of the test compounds, positive control and diluent were applied to additional skin areas to serve as unirradiated control sites. Application areas were checked for skin irritation at 24, 48 and 72 hours.	Positive control application and irradiation caused greater irritant effects than in unirradiated skin areas.	

Study Nos. 75-51-0833-80, 75-51-0834-80, 75-51-0835-80, Oct 75 - Apr 80

Test	Results	Interpretation
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SENSITIZATION STUDIES

Guinea Pigs (Male)

Intradermal injections of 0.1 mL of a 0.1 percent solution (w/v) of the compounds or of dinitrochlorobenzene (DNCB)* in a mixture containing 1 volume of propylene glycol and 29 volumes of saline.

Ten test guinea pigs were given 10 sensitizing doses over a 3-week period. After 2 weeks rest, they were challenged with ID injections of test compound.

None of the compound challenge doses produced a sensitization reaction.

None of these test compounds produced a sensitization reaction under test conditions and none are expected to produce a sensitization reaction in man.

Ten positive control guinea pigs were sensitized over 3 weeks with DNCB. After 2 weeks rest, they were challenged with ID injections of DNCB.

Challenge dose of DNCB in positive control pigs produced a marked sensitization reaction in 10 out of 10 guinea pigs.

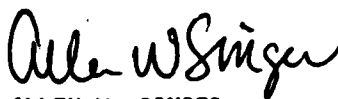
DNCB produce a marked reaction, indicating the guinea pigs respond to sensitizing agents.

* A known skin sensitizer.

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5. CONCLUSION. Technical grade compounds AI3-36325 and AI3-36328 caused moderate corneal and conjunctival irritations; AI3-36326 cause a similar, but milder, irritation. AI3-36326 and AI3-36328 caused mild primary skin irritation when applied neat; AI3-36325 and AI3-36326 caused a similar reaction when applied as a 25 percent weight-volume solution in ethanol.

6. RECOMMENDATION. Under the provisions of the Memorandum of Understanding (paragraph 1b), it is recommended that individuals using these compounds be cautioned to restrict use from the face and eyes.



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CPT, VC

Laboratory Animal Veterinary Officer
Toxicology Division

APPROVED:



ARTHUR H. MCCREESH, Ph.D.
Chief, Toxicology Division

APPENDIX

TOPICAL HAZARD EVALUATION PROGRAM
DEFINITIONS OF CATEGORIES OF COMPOUNDS BEING
CONSIDERED FOR ACUTE SKIN APPLICATION

CATEGORY I - Compounds producing no primary irritation of the intact skin or no greater than mild primary irritation of the skin surrounding an abrasion. (INTERPRETATION: No restriction for acute application to the human skin.)

CATEGORY II - Compounds producing mild primary irritation of the intact skin and the skin surrounding an abrasion. (INTERPRETATION: Should be used only on human skin found by examination to have no abrasions or may be used as a clothing impregnant.)

CATEGORY III - Compounds producing moderate primary irritation of the intact skin and the skin surrounding an abrasion. (INTERPRETATION: Should not be used directly on the skin without a prophetic patch test having been conducted on humans to determine irritation potential to human skin. May be used without patch testing, with extreme caution, as clothing impregnants. Compound should be resubmitted in the form and at the intended use concentration so that its irritation potential can be reexamined using other test techniques on animals.)

CATEGORY IV - Compounds producing moderate to severe primary irritation of the intact skin and of the skin surrounding an abrasion and, in addition, producing necrosis, vesiculation, and/or eschars. (INTERPRETATION: Should be resubmitted for testing in the form and at the intended use concentration. Upon resubmission, its irritation potential will be reexamined using other test techniques on animals, prior to possible prophetic patch testing in humans, at concentrations which have been shown not to produce primary irritation in animals.)

CATEGORY V - Compounds impossible to classify because of staining of the skin or other masking effects owing to physical properties of the compound. (INTERPRETATION: Not suitable for use on humans.)

EYE CATEGORIES:

A. Compounds noninjurious to the eye. INTERPRETATION: Irritation of human eyes is not expected if the compound should accidentally get into the eyes, provided it is washed out as soon as possible.

B. Compounds producing mild injury to the cornea. INTERPRETATION: Should be used with caution around the eyes.

C. Compounds producing mild injury to the cornea, and in addition some injury to the conjunctiva. INTERPRETATION: Should be used with caution around the eyes and mucosa.

D. Compounds producing moderate injury to the cornea. INTERPRETATION: Should be used with extreme caution around the eyes.

E. Compounds producing moderate injury to the cornea, and in addition producing some injury to the conjunctiva. INTERPRETATION: Should be used with extreme caution around the eyes and mucosa.

F. Compounds producing severe injury to the cornea and to the conjunctiva. INTERPRETATION: Should be used with extreme caution. It is recommended that use be restricted to areas other than the face.